PM PA Review

Comments on Chapter 1

Tony Cox

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Some stated goals for the PM PA

1. Facilitate CASAC advice to the Agency and recommendations to the Administrator
2. Serve as a source of policy-relevant information
3. Be understandable to a broad audience

Making the PA useful

- *Policy relevance:* Summarize what is and what is not known about how changing exposure changes human health risks
  - Evidence from intervention studies (e.g., Burns et al 2019)
    - Characterize uncertainty, sensitivity, heterogeneity of causal C-R
  - Systematic, transparent summary of *all* causally relevant evidence and plausible alternative interpretations
    - Neutral information provider ("honest broker") vs. advocacy roles
    - Negative (e.g., Geven et al., Burns et al.) as well as positive evidence
- *Broad understandability* requires:
  - Clear definitions of key terms and quantities (e.g., β) used to derive and communicate results
  - Transparency in selecting, evaluating, interpreting, and summarizing/synthesizing studies
    - Explicit rules, systematically applied
  - Explicit, checkable derivations of conclusions from data

Key question for CASAC

- What does current sound scientific evidence imply for whether current NAAQS must be revised to protect human health with an adequate margin of safety?
  - Would a change produce desired results?
    - Would it do more good than harm?
  - How sure are we? Why?
    - Explicit justification based on data, not opinion
  - What uncertainties/sensitivities/research needs remain?
  - How should they be addressed?
- The CASAC's answer should be based on sound science
  - Goal: Support conclusions with explicit justifications/ derivations based on relevant data, not opinion

What makes a scientific argument "sound"?

- Are stated conclusions implied by their premises?
  - Premises = data + assumptions
  - Assumptions should be explicitly stated
- Are the premises correct?
  - Reproducible observations?
  - Reproducible tests of assumptions?
- Should other data/evidence be considered?
- Are the conclusions policy-relevant?
- Are conclusions clearly stated and properly caveated?
  - No over-generalization
  - Dependence on ay untested assumptions made clear
  - Sound quantitative uncertainty and sensitivity analyses

Practical principles of sound science

- ***Clarity:*** **Provide explicit, clear, operational definitions of all key terms used to communicate results.**
  - Give operational definitions for causal determination categories
  - Does "Causal" mean that reducing exposure would reduce risk? (By at least a certain amount, for at least some fraction of the population?)
- ***Transparency:*** **Provide explicit, transparent, logically sound derivations of conclusions from data**
  - Judgment ≠ derivation; association ≠ causation; assumption ≠ evidence
- ***Reproducibility :*** **Report results of reproducible tests of predictions against observations (e.g., using formal hypothesis testing)**
  - Test relevant null hypotheses (e.g., are health outcomes conditionally independent of exposure, given covariates in adjustment sets?)
- ***Objectivity:*** **Follow explicit, systematic procedures for selecting and evaluating individual studies and deriving conclusions from them**
  - Report results of evaluations in transparent, systematic summaries.
  - Carefully qualify causal interpretations and conclusions to acknowledge and communicate remaining ambiguities, uncertainties, or conflicts in evidence
  - Avoid over-generalizations and subjective interpretations
  - Discuss plausible alternative interpretations

www.nap.edu/read/1864/chapter/4#39 Responsible Science: Ensuring the Integrity of the Research Process, Vol. 1

An unsound argument

- *Observed association:* More heat stroke deaths occur on days when ice cream sales are high than on days when they are low.
  - $\beta > 0$ extra deaths per 10 oz increment of ice cream sold
- *Unsound causal inference:* Ice cream kills! Each 10 oz increment of ice cream is linked to $\beta > 0$ extra deaths
- *Unsound policy implication:* To reduce mortality risk, we must reduce exposure to ice cream
  - Simulation model: β premature deaths avoided per 10 oz reduction in ice cream
  - Empirical experience: Reducing ice cream sales has not yet clearly reduced mortality rates.
    - Unsound interpretation: Low exposures to ice cream is even more dangerous than previously estimated (supralinear dose-response).
- Logical Problem: Association is not causation

Logical unsoundness of argument is independent of specific content

- *Observed association:* More deaths occur on days when PM2.5 concentrations are high than on days when they are low.
  - $\beta > 0$ extra deaths per 10 $\mu g/m^3$ increment of PM2.5
- *Unsound causal inference:* PM2.5 kills! Each 10 $\mu g/m^3$ increment of PM2.5 is linked to $\beta > 0$ extra deaths
- *Unsound policy implication:* To reduce mortality risk, we must reduce exposure to PM2.5
  - Simulation model: β premature deaths avoided per 10 $\mu g/m^3$ reduction in PM2.5
  - Empirical experience: Reducing PM2.5 has not yet clearly reduced mortality rates.
    - Unsound interpretation: Low exposures to PM2.5 is even more dangerous than previously estimated (supralinear dose-response).
- Logical Problem: Association is not causation. (Really!)

Science and risk analysis questions

- How would simulated results in the PA change if the C-R functions were corrected for…
  - Confounding? (E.g., daily high and low temperatures)
  - Measurement errors & exposure estimation errors?
  - Modeling biases, p-hacking?
  - More recent and relevant literature?
- What *alternative underlying interpretations* are consistent with the scientific evidence? To what extent do they support alternative standards?
- Taking into account the answers to the preceding questions, *what does currently available scientific evidence show about whether and how much changes in current exposures would affect public health risks?*

Science and risk analysis questions

- How would simulated results in the PA change if C-R functions were corrected for *confounding?*
  - Daily high and low temperatures
    - Lags 0-30 days (empirically determined)
  - Socioeconomic variables
  - Others?
- Answers should be clear and explicit in PA
  - Not implicit in assumptions and interpretations of β
- Answers are not given in the Draft PA
  - None of the 8 key studies that drive simulated results includes daily high and low temperatures
  - Some collected the data, but then averaged it

Science and risk analysis questions

- How would simulated results in the PA change if C-R functions were corrected for *exposure estimation errors?*
  - To what extent are effects associated with high concentrations attributed to lower concentrations?
  - How much wider would confidence intervals be if exposure estimation error were included?
  - Cox PH model requires adjustment for covariate measurement errors. These were not made.

Science and risk analysis questions

- How would simulated results in the PA change if C-R functions were corrected for *modeling biases and p-hacking?*
  - Regression diagnostics omitted
  - Model uncertainty omitted $\rightarrow$ confidence intervals too narrow

Science and risk analysis questions

- How would simulated results in the PA change if C-R functions were revised to include more *recent and relevant literature?*
  - Intervention and accountability studies

Omitted evidence: Henneman et al. (2017)

- "Multiple studies in the accountability field have found it **difficult to attribute significant improvements** in air quality or public health attributable to air quality regulations … This difficulty [is] particularly prevalent in studies that **diligently control for multiple confounders** across domains (location, time, etc.)"

- "…Often, one study will assess a regulatory action and determine that the intervention led to a statistically significant change in the response of interest… Later, using additional data, updated methods, and/or **accounting for additional factors, those results are found to be less definitive and potentially invalid**"

Omitted evidence: Burns et al. (2019)

- "It was **difficult to derive overall conclusions** regarding the effectiveness of interventions in terms of improved air quality or health.
- Most included studies observed either **no significant association** in either direction or an association favouring the intervention, with little evidence that the assessed interventions might be harmful.
- The evidence base highlights the **challenges related to establishing a causal relationship** between specific air pollution interventions and outcomes."
- Contrast with PA, p. 3-7: *"…Evidence was sufficient to conclude a causal relationship exists between PM2.5 exposures and mortality and cardiovascular effects (i.e., for both long- and short-term exposures)*"

Omitted caveats

- "This sort of study can provide useful estimates, but the figures are only based on theoretical models. In particular, although particles of pollution have been associated with premature mortality in other studies, **a definitive causative link has not yet been demonstrated**." www.nhs.uk/news/2012/04april/Pages/air-pollution-exhaust-death-estimates.aspx

Challenge for CASAC deliberation

- Given that
  - Absence of evidence is not necessarily evidence of absence
    - but it may imply upper bounds on plausible effects sizes
  - "Associations are not effects" (Pettiti 1991)
  - Correlation is not causation
- What can we conclude *and justify via explicit sound science derivations* about how changes in PM2.5 affect human health risks?
  - What have effects of past interventions been?
  - What effects should potential alternative future interventions be expected to have? How certain?

8 key studies, overlapping coauthors. All address association, not causation.

Table 3-4. Epidemiologic studies used to estimate $PM_{2.5}$-associated risk.

Epidemiology Study	Study Population[a]	Age Range (years)	Mortality Categories Covered
Long-term mortality studies			
Jerrett et al., 2016	ACS	30+	IHD
Pope et al., 2015	ACS	30+	All-cause, IHD
Turner et al., 2016	ACS	30+	Lung cancer
Thurston et al., 2016	AARP	55-85	All-cause
Di et al., 2017b	Medicare	65+	All-cause
Short-term mortality			
Baxter et al., 2017	77 cities	All ages	Non-accidental
Ito et al., 2013	NPACT	All ages	All cause
Zanobetti et al., 2014	121 communities	65+	All cause

[a]ACS (American Cancer Survey), AARP (American Association of Retired Persons), NPACT (National Particle Components Toxicity). See Appendix C Table C-1 for additional study details.

Comparing the Health Effects of Ambient Particulate Matter Estimated Using Ground-Based versus Remote Sensing Exposure Estimates

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Background: Remote sensing (RS) is increasingly used for exposure assessment in epidemiological and burden of disease studies, including those investigating whether chronic exposure to ambient fine particulate matter ($PM_{2.5}$) is associated with mortality.

Objectives: We compared relative risk estimates of mortality from diseases of the circulatory system for $PM_{2.5}$ modeled from RS with that for $PM_{2.5}$ modeled using ground-level information.

Methods: We geocoded the baseline residence of 668,629 American Cancer Society Cancer Prevention Study II (CPS-II) cohort participants followed from 1982 to 2004 and assigned $PM_{2.5}$ levels to all participants using seven different exposure models. Most of the exposure models were averaged for the years 2002–2004, and one RS estimate was for a longer, contemporaneous period. We used Cox proportional hazards regression to estimate relative risks (RRs) for the association of $PM_{2.5}$ with circulatory mortality and ischemic heart disease.

Results: Estimates of mortality risk differed among exposure models. The smallest relative risk was observed for the RS estimates that excluded ground-based monitors for circulatory deaths [RR = 1.02, 95% confidence interval (CI): 1.00, 1.04 per 10 $\mu g/m^3$ increment in $PM_{2.5}$]. The largest relative risk was observed for the land-use regression model that included traffic information (RR = 1.14, 95% CI: 1.11, 1.17 per 10 $\mu g/m^3$ increment in $PM_{2.5}$).

Conclusions: We found significant associations between $PM_{2.5}$ and mortality in every model; however, relative risks estimated from exposure models using ground-based information were generally larger than those estimated using RS alone.

associated with $PM_{2.5}$ (Evans et al. 2013; Lim et al. 2012).

A few studies have attempted to systematically compare the exposure estimates from ground-based versus RS models. Lee et al.

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Temperature? Measurement error? Regression diagnostics?

Clinical Track

Relationships Between Fine Particulate Air Pollution, Cardiometabolic Disorders, and Cardiovascular Mortality

C. Arden Pope III, Michelle C. Turner, Richard T. Burnett, Michael Jerrett, Susan M. Gapstur, W. Ryan Diver, Daniel Krewski, Robert D. Brook

Rationale: **Growing evidence suggests that long-term exposure to fine particulate matter ($PM_{2.5}$) air pollution contributes to risk of cardiovascular disease (CVD) morbidity and mortality. There is uncertainty about who are most susceptible. Individuals with underlying cardiometabolic disorders, including hypertension, diabetes mellitus, and obesity, may be at greater risk. $PM_{2.5}$ pollution may also contribute to cardiometabolic disorders, augmenting CVD risk.**

Objective: **This analysis evaluates relationships between long-term $PM_{2.5}$ exposure and cardiometabolic disease on risk of death from CVD and cardiometabolic conditions.**

Methods and Results: **Data on 669 046 participants from the American Cancer Society Cancer Prevention Study II cohort were linked to modeled $PM_{2.5}$ concentrations at geocoded home addresses. Cox proportional hazards regression models were used to estimate adjusted hazards ratios for death from CVD and cardiometabolic diseases based on death-certificate information. Effect modification by pre-existing cardiometabolic risk factors on the $PM_{2.5}$–CVD mortality association was examined. $PM_{2.5}$ exposure was associated with CVD mortality, with the hazards ratios (95% confidence interval) per 10 $\mu g/m^3$ increase in $PM_{2.5}$ equal to 1.12 (1.10–1.15). Deaths linked to hypertension and diabetes mellitus (mentioned on death certificate as either primary or contributing cause of death) were also associated with $PM_{2.5}$. There was no consistent evidence of effect modification by cardiometabolic disease risk factors on the $PM_{2.5}$–CVD mortality association.**

X ***Conclusions:*** **Pollution-induced CVD mortality risk is observed for those with and without existing cardiometabolic disorders. Long-term exposure may also contribute to the development or exacerbation of cardiometabolic disorders, increasing risk of CVD, and cardiometabolic disease mortality. (*Circ Res*. 2015;116:108-115. DOI: 10.1161/CIRCRESAHA.116.305060.)**

ORIGINAL ARTICLE

Long-Term Ozone Exposure and Mortality in a Large Prospective Study

Michelle C. Turner[1,2,3,4], Michael Jerrett[5], C. Arden Pope III[6], Daniel Krewski[1,7], Susan M. Gapstur[8], W. Ryan Diver[8], Bernardo S. Beckerman[5], Julian D. Marshall[9], Jason Su[5], Daniel L. Crouse[10], and Richard T. Burnett[11]

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Abstract

Rationale: Tropospheric ozone (O_3) is potentially associated with cardiovascular disease risk and premature death. Results from long-term epidemiological studies on O_3 are scarce and inconclusive.

Objectives: In this study, we examined associations between chronic ambient O_3 exposure and all-cause and cause-specific mortality in a large cohort of U.S. adults.

Methods: Cancer Prevention Study II participants were enrolled in 1982. A total of 669,046 participants were analyzed, among whom 237,201 deaths occurred through 2004. We obtained estimates of O_3 concentrations at the participant's residence from a hierarchical Bayesian space–time model. Estimates of fine particulate matter (particulate matter with an aerodynamic diameter of up to 2.5 μm [$PM_{2.5}$]) and NO_2 concentrations were obtained from land use regression. Cox proportional hazards regression models were used to examine mortality associations adjusted for individual- and ecological-level covariates.

Measurements and Main Results: In single-pollutant models, we observed significant positive associations between O_3, $PM_{2.5}$, and NO_2 concentrations and all-cause and cause-specific mortality. In two-pollutant models adjusted for $PM_{2.5}$, significant positive associations remained between O_3 and all-cause (hazard ratio [HR] per 10 ppb, 1.02; 95% confidence interval [CI], 1.01–1.04), circulatory (HR, 1.03; 95% CI, 1.01–1.05), and respiratory mortality (HR, 1.12; 95% CI, 1.08–1.16) that were unchanged with further adjustment for NO_2. We also observed positive mortality associations with both $PM_{2.5}$ (both near source and regional) and NO_2 in multipollutant models.

Conclusions: Findings derived from this large-scale prospective study suggest that long-term ambient O_3 contributes to risk of respiratory and circulatory mortality. Substantial health and environmental benefits may be achieved by implementing further measures aimed at controlling O_3 concentrations.

X

Keywords: air pollution; mortality; ozone; prospective study

Incomplete control for confounding

- *"We examined potential confounding by elevation, metropolitan statistical area size, annual average daily maximum air temperature, and 1980 percentage of air conditioning… We used Cox proportional hazards regression models to examine associations between mean O3 (2002–2004), PM2.5 (1999–2004), and NO2 (2006) concentrations and all-cause and cause specific mortality." (Turner et al. 2016)*
  - Residual confounding
    - Monthly and weekly average daily high (and low) temperatures?
  - Omitted confounders
    - Daily low temperatures?
    - Lagged daily high and low temperatures?

Temperature? Measurement error? Regression diagnostics?

Ambient Particulate Matter Air Pollution Exposure and Mortality in the NIH-AARP Diet and Health Cohort

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Background: Outdoor fine particulate matter (≤ 2.5 μm; $PM_{2.5}$) has been identified as a global health threat, but the number of large U.S. prospective cohort studies with individual participant data remains limited, especially at lower recent exposures.

Objectives: We aimed to test the relationship between long-term exposure $PM_{2.5}$ and death risk from all nonaccidental causes, cardiovascular (CVD), and respiratory diseases in 517,041 men and women enrolled in the National Institutes of Health-AARP cohort.

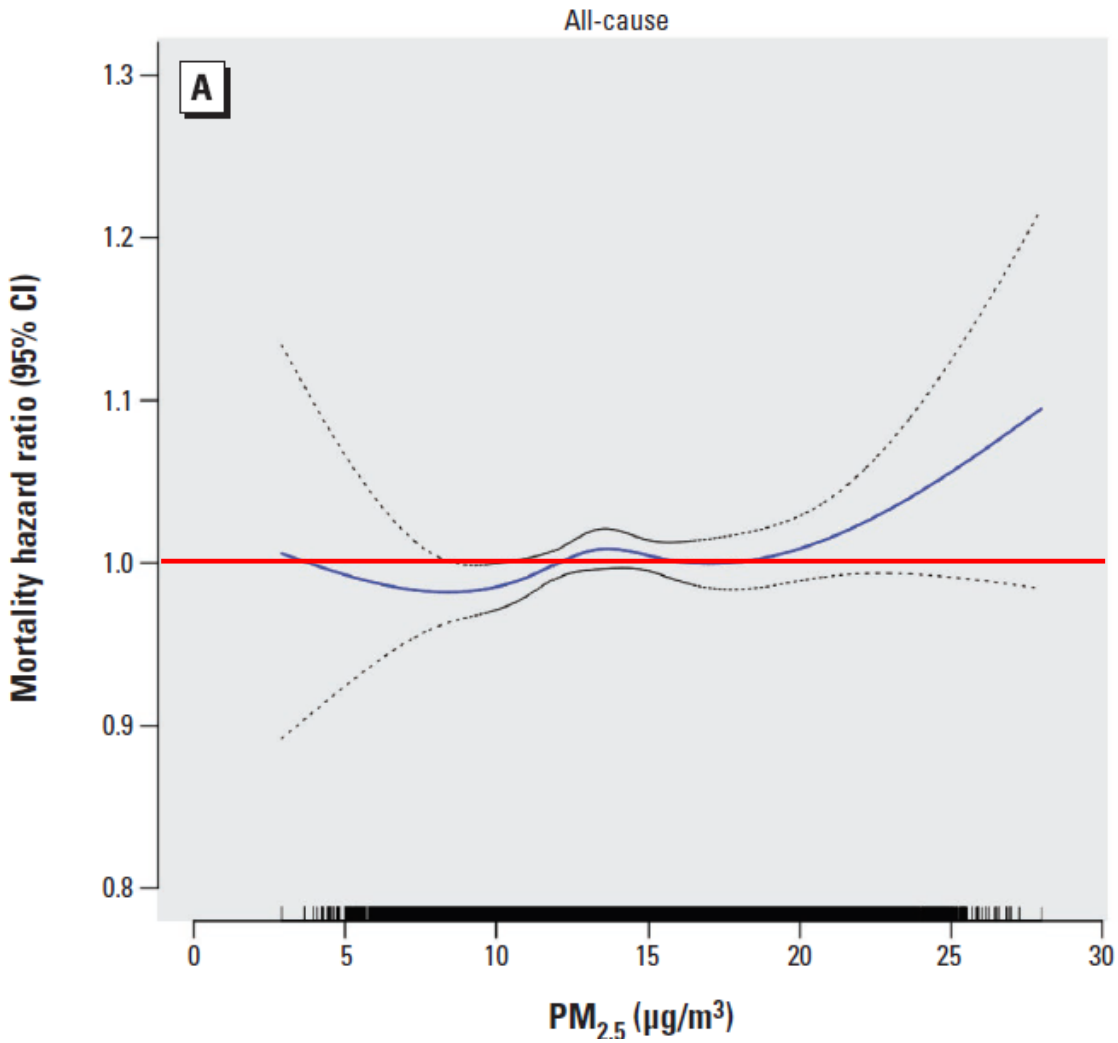
Methods: Individual participant data were linked with residence $PM_{2.5}$ exposure estimates across the continental United States for a 2000–2009 follow-up period when matching census tract–level $PM_{2.5}$ exposure data were available. Participants enrolled ranged from 50 to 71 years of age, residing in six U.S. states and two cities. Cox proportional hazard models yielded hazard ratio (HR) estimates per 10 μg/m^3 of $PM_{2.5}$ exposure.

Results: $PM_{2.5}$ exposure was significantly associated with total mortality (HR = 1.03; 95% CI: 1.00, 1.05) and CVD mortality (HR = 1.10; 95% CI: 1.05, 1.15), but the association with respiratory mortality was not statistically significant (HR = 1.05; 95% CI: 0.98, 1.13). A significant association was found with respiratory mortality only among never smokers (HR = 1.27; 95% CI: 1.03, 1.56). Associations with 10-μg/m^3 $PM_{2.5}$ exposures in yearly participant residential annual mean, or in metropolitan area-wide mean, were consistent with baseline exposure model results. Associations with $PM_{2.5}$ were similar when adjusted for ozone exposures. Analyses of California residents alone also yielded statistically significant $PM_{2.5}$ mortality HRs for total and CVD mortality.

Conclusions: Long-term exposure to $PM_{2.5}$ air pollution was associated with an increased risk of total and CVD mortality, providing an independent test of the $PM_{2.5}$–mortality relationship in a new large U.S. prospective cohort experiencing lower post-2000 $PM_{2.5}$ exposure levels.

questionnaire in 1995 and 1996. Details of the NIH-AARP Study have been described previously (Schatzkin et al. 2001). Among 566,398 participants enrolled in the NIH-AARP cohort and available for analysis in 2014, we first excluded for this analysis those individuals for whom the forms were filled out by a proxy (n = 15,760, or 2.8%); who moved out of their study region before January 2000 (n = 13,863, or 2.4%); who died before 1 January 2000 (n = 21,415, or 3.8%); and those for whom census-level outdoor $PM_{2.5}$ exposure was not estimable using the methods discussed below (n = 737, or 0.1%). After accounting for overlapping exclusions, the analytic cohort includes 517,041 (91.3%) participants for whom matching $PM_{2.5}$ air pollution data were available. The NIH-AARP cohort questionnaires elicited information on demographic and anthropometric characteristics, dietary intake, and numerous health-related variables (e.g., marital status, body mass index, educa-

Thurston et al. 2016



"Figure 2 graphically demonstrates, for the time-independent model, the **monotonically rising** nature of the concentration–response curve for both all-cause and CVD mortality (vs. a referent HR = 1.0 at the mean level of exposure)." *X*

Red horizontal line added at HR = 1.0 for comparison

"Monotonically rising" segment (not significant) starts at about 18 µg/m^3

PA: Simulate assuming monotonic increase at all exposure concentrations

Reference and study title	Study description	Exposure Estimation Approach	CR function model	Location of study effect estimate(s) in journal article	Additional notes regarding effect estimate selection	Epidemiologic statistic	Mortality endpoint	Selected effect estimate	Selected beta	Selected beta standard error (SE)
Cardiovascular Mortality	- ACS (30+) (oversampled affluent individuals) - individual-level covariates				NA	Hazard ratio (95 percent CI)	IHD	1.14 (1.1-1.18)	1.31E-02	1.79E-03
Thurston et al., 2016 Ambient Particulate Matter Air Pollution Exposure and Mortality in the NIH-AARP Diet and Health Cohort	Reevaluates the relationship between long-term exposure to ambient $PM_{2.5}$ and mortality given recent decline in U.S. ambient PM concentrations. Differentiation of risk for fossil fuel $PM_{2.5}$ versus total $PM_{2.5}$ - NIH-AARP Cohort (only select states - CA, FL, LA, NJ, NC, PA, GA MI) (55-85yrs) - CVD, all-cause - residential locations matched to census tract-level $PM_{2.5}$ estimates	Exposures estimated at census tract centroids based on land use data and ground-based monitors	Cox proportional hazard model	Table 2. NIH-AARP cohort time independent Cox model $PM_{2.5}$ mortality hazard ratios (and 95th percentile CI) per 10 $\mu g/m^3$, by cause and cohort subgroup. Cohort: ALL	NA	Hazard ratio (95 percent CI)	All-cause	1.03 (1-1.05)	2.96E-03	1.24E-03
Turner et al., 2016 Long-Term Ozone Exposure and Mortality in a Large Prospective Study	Evaluates the relationship between long-term exposure to ambient $PM_{2.5}$ and all-cause and cause-specific mortality. Also, estimated the association between $PM_{2.5}$, regional $PM_{2.5}$, and near-source $PM_{2.5}$ and mortality in single-pollutant, copollutant and multipollutant models. - ACS (30+) - Includes lung cancer (otherwise similar results to Pope et al., 2015) - county-level assessment	Exposures estimated at residential locations based on land use data and ground-based monitors	Cox proportional hazard model	Table E4. Adjusted HRs (95th percentile CI) for all-cause and cause-specific mortality in relation to each 10 unit increase in $PM_{2.5}$ LUR-BME concentrations, follow-up 1982-2004, CPS-II cohort, United States (n = 669,046).	Note that the non-cancer mortality endpoints provided in table E4 appear to mirror those provided in Table 1 of Pope et al., 2015 - so will use long-cancer effect estimate from this study only.	Hazard ratio (95 percent CI)	Lung cancer	1.09 (1.03-1.16)	8.62E-03	3.03E-03
	Short-term exposure-related mortality studies									

Di et al. (2017)

- *"Annual averages [of PM2.5 and O3] were estimated according to the ZIP Code of residence for each enrollee. …For each calendar year during which a person was at risk of death, we assigned to that person a value for the annual average $PM_{2.5}$ concentration, a value for average ozone level during the warm season (April 1 through September 30), and values for annual average temperature and humidity according to the ZIP Code of the person's residence."*
- Residual confounding?
  - Daily high and low temperatures and PM2.5 levels?
- Correction for measurement error?
- Regression diagnostics?

Influence of exposure differences on city-to-city heterogeneity in $PM_{2.5}$-mortality associations in US cities

Lisa K. Baxter[1*], James L. Crooks[1,3,4] and Jason D. Sacks[2]

Abstract

Background: Multi-city population-based epidemiological studies have observed heterogeneity between city-specific fine particulate matter ($PM_{2.5}$)-mortality effect estimates. These studies typically use ambient monitoring data as a surrogate for exposure leading to potential exposure misclassification. The level of exposure misclassification can differ by city affecting the observed health effect estimate.

Methods: The objective of this analysis is to evaluate whether previously developed residential infiltration-based city clusters can explain city-to-city heterogeneity in $PM_{2.5}$ mortality risk estimates. In a prior paper 94 cities were clustered based on residential infiltration factors (e.g. home age/size, prevalence of air conditioning (AC)), resulting in 5 clusters. For this analysis, the association between $PM_{2.5}$ and all-cause mortality was first determined in 77 cities across the United States for 2001–2005. Next, a second stage analysis was conducted evaluating the influence of cluster assignment on heterogeneity in the risk estimates.

Results: Associations between a 2-day (lag 0–1 days) moving average of $PM_{2.5}$ concentrations and non-accidental mortality were determined for each city. Estimated effects ranged from −3.2 to 5.1% with a pooled estimate of 0.33% (95% CI: 0.13, 0.53) increase in mortality per 10 μg/m^3 increase in $PM_{2.5}$. The second stage analysis determined that cluster assignment was marginally significant in explaining the city-to-city heterogeneity. The health effects estimates in cities with older, smaller homes with less AC (Cluster 1) and cities with newer, smaller homes with a large prevalence of AC (Cluster 3) were significantly lower than the cluster consisting of cities with older, larger homes with a small percentage of AC.

Conclusions: This is the first study that attempted to examine whether multiple exposure factors could explain the heterogeneity in $PM_{2.5}$-mortality associations. The results of this study were found to explain a small portion (6%) of this heterogeneity.

Keywords: Particulate matter, Epidemiology, Exposure, Meta-regression, Cluster analysis

Draft PA: Ignore negative effects and heterogeneity

Reference and study title	Study description	Exposure Estimation Approach	CR function model	Location of study effect estimate(s) in journal article	Additional notes regarding effect estimate selection	Epidemiologic statistic	Mortality endpoint	Selected effect estimate	Selected beta	Selected beta standard error (SE)
Baxter et al., 2017 Influence of exposure differences in city-to-city heterogeneity in $PM_{2.5}$-mortality associations in U.S. cities	Uses cluster-based approach to evaluate the impact of residential infiltration factors on inter-city heterogeneity in short-term PM-mortality associations. - Mortality data from NCHS - 77 U.S. CBSAs (all ages) - non-accidental mortality - CBSA-level assessment	Exposure estimates based on data from ground-based monitors	Poisson (log-linear) at city-level then aggregated	Obtained from results section in the text. After pooling the city-specific effect estimates into an overall effect estimate, short-term $PM_{2.5}$ exposure was found to increase 24-hr non-accidental mortality by 0.33% (95% CI: 0.13, 0.53). Based on lag 2 (day 0-1)	NA	Percent increase in 24-hr mortality (95 percent CI)	24-hr non-accidental mortality	0.33 (0.13-0.53)	3.29E-04	1.02E-04
Ito et al., 2013 NPACT study 3. Time-series analysis of mortality, hospitalizations, and ambient $PM_{2.5}$ and its components	Use factor analysis to characterize pollution sources, assess the association between $PM_{2.5}$ and $PM_{2.5}$ components with morbidity and mortality outcomes. Also evaluates pollution levels, land-use, and other variables as modifiers that may explain inter-city variation in PM-mortality effect estimates. - Mortality data from NCHS - 150 and 64 U.S. cities (two analyses) (all ages) - MSA-level assessment	Exposure estimates based on data from ground-based monitors	Poisson GLM	Appendix G, Table G.6 for Figure 4 - use all-year lag 1 Beta: Regression coefficients (beta) and their SE for air pollutants at lag 0 through 3 days used to compute percent excess risks in figures shown in the main text and in Appendices B and G (corresponding figures are noted).	Utilized lag-1 (all year) beta because that had the strongest effect for CVD mortality and wanted our all-cause to reflect that stronger lag-association for the CVD effect (even though focusing on all-cause)	Betas with SE (no conversion required)	24-hr all-cause mortality	Study provided beta and SE	1.45E-04	7.47E-05

Ito, Ross, Zhou, Nádas, Lippman, Thurston (HEI Report 177)

- HEI Review Panel Comments: "The Review Panel appreciated the need to simplify but was disappointed that other approaches were not considered. Because of the large numbers of associations estimated, 5% of the results would be expected to be significant by chance alone; that is, false positive or false negative associations. If we add to this the percentage of false positive and negative associations that may be expected as a result of biases, it is clear that **chance or bias may be a possible explanation for any significant association reported here**. Compounding these issues is the fact that **the investigators made little note of statistically significant associations that were negative while focusing on the statistically significant positive associations**. The investigators' explanation that weekly patterns may produce the inverse associations observed for pollution at 1-day lag is not convincing and could indicate a problem with the statistical model or with the sparse data…"

Draft PA: Use a positive beta

Reference and study title	Study description	Exposure Estimation Approach	CR function model	Location of study effect estimate(s) in journal article	Additional notes regarding effect estimate selection	Epidemiologic statistic	Mortality endpoint	Selected effect estimate	Selected beta	Selected beta standard error (SE)
Baxter et al., 2017 Influence of exposure differences in city-to-city heterogeneity in $PM_{2.5}$-mortality associations in U.S. cities	Uses cluster-based approach to evaluate the impact of residential infiltration factors on inter-city heterogeneity in short-term PM-mortality associations. - Mortality data from NCHS - 77 U.S. CBSAs (all ages) - non-accidental mortality - CBSA-level assessment	Exposure estimates based on data from ground-based monitors	Poisson (log-linear) at city-level then aggregated	Obtained from results section in the text. After pooling the city-specific effect estimates into an overall effect estimate, short-term $PM_{2.5}$ exposure was found to increase 24-hr non-accidental mortality by 0.33% (95% CI: 0.13, 0.53). Based on lag 2 (day 0-1)	NA	Percent increase in 24-hr mortality (95 percent CI)	24-hr non-accidental mortality	0.33 (0.13-0.53)	3.29E-04	1.02E-04
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Temperature? Measurement error? Regression diagnostics?

- Zanobetti et al.: "We applied a conditional logistic regression controlling for day of the week and weather. To control for the potential confounding by weather, we included into the regression model average temperature for the same and previous day."
  - Daily high/low temperatures?
  - Lags > 1 day?

Zanobetti *et al. Environmental Health* 2014, **13**:38
http://www.ehjournal.net/content/13/1/38

ENVIRONMENTAL HEALTH

RESEARCH Open Access

A national case-crossover analysis of the short-term effect of $PM_{2.5}$ on hospitalizations and mortality in subjects with diabetes and neurological disorders

Antonella Zanobetti[1*], Francesca Dominici[2], Yun Wang[2] and Joel D Schwartz[1]

Abstract

Background: Diabetes and neurological disorders are a growing burden among the elderly, and may also make them more susceptible to particulate air matter with aerodynamic diameter less than 2.5 μg ($PM_{2.5}$). The same biological responses thought to effect cardiovascular disease through air pollution-mediated systemic oxidative stress, inflammation and cerebrovascular dysfunction could also be relevant for diabetes and neurodegenerative diseases.

Methods: We conducted multi-site case-crossover analyses of all-cause deaths and of hospitalizations for diabetes or neurological disorders among Medicare enrollees (>65 years) during the period 1999 to 2010 in 121 US communities. We examined whether 1) short-term exposure to $PM_{2.5}$ increases the risk of hospitalization for diabetes or neurological disorders, and 2) the association between short-term exposure to $PM_{2.5}$ and all-cause mortality is modified by having a previous hospitalization of diabetes or neurological disorders.

Results: We found that short term exposure to $PM_{2.5}$ is significantly associated with an increase in hospitalization risks for diabetes (1.14% increase, 95% CI: 0.56, 1.73 for a 10 μg/m^3 increase in the 2 days average), and for Parkinson's disease (3.23%, 1.08, 5.43); we also found an increase in all-cause mortality risks (0.64%, 95% CI: 0.42, 0.85), but we didn't find that hospitalization for diabetes and neurodegenerative diseases modifies the association between short term exposure to $PM_{2.5}$ and all-cause mortality.

Conclusion: We found that short-term exposure to fine particles increased the risk of hospitalizations for Parkinson's disease and diabetes, and of all-cause mortality. While the association between short term exposure to $PM_{2.5}$ and mortality was higher among Medicare enrollees that had a previous admission for diabetes and neurological disorders than among Medicare enrollees that did not had a prior admission for these diseases, the effect modification was not statistically significant. We believe that these results provide useful insights regarding the mechanisms by which particles may affect the brain. A better understanding of the mechanisms will enable the development of new strategies to protect individuals at risk and to reduce detrimental effects of air pollution on the nervous system.

Keywords: $PM_{2.5}$, Diabetes, Neurological disorders, Mortality risk, Hospitalizations

X

Common methodological limitations of the 8 selected key studies

- Incomplete control for confounding (e.g., temp.)
- Exposure estimation errors ignored
  - Distorts estimated C-R function, obscures thresholds
- Modeling biases not quantified
  - No regression diagnostics
- Association studies, not designed or analyzed to permit valid causal inferences
- ***Conclusion:*** *It is not sound science to use associations from these studies to simulate or predict effects on health risks of changing PM2.5.*
  - β coefficients in Table C-1 are not valid for this use
  - See comments from external consultants

Predictive validity is essential for sound science

- Main gap in PM2.5 PA now is providing sound, reliable, *validated* information about how interventions that reduce PM2.5 affect public health risks
- In the short run, this gap might be closed by considering recent evidence from intervention studies (e.g., Burns 2019)
- Longer run: Develop, *validate*, and apply predictive causal models

Assessing the Predictive Validity of Strength of Evidence Grades: A Meta-Epidemiological Study

Structured Abstract

Objective. We sought to determine the predictive validity of the U.S. Evidence-based Practice Center (EPC) approach to GRADE (Grading of Recommendations Assessment, Development and Evaluation) by examining how reliably it can predict the likelihood that treatment effects remain stable as new studies emerge.

Study design and setting. Based on 37 Cochrane reports with outcomes graded as high strength of evidence (SOE), we prepared 160 documents using portions of these bodies of evidence in a chronological order. We randomly assigned these documents, which represented different levels of SOE, to professional systematic reviewers from seven academic centers in Austria, Canada, and the United States, who dually graded the SOE using guidance for the EPC program. For each of the 160 documents, we determined whether estimates remained stable as subsequent studies were added to the evidence base. For each grade of SOE, we compared the observed proportion of stable estimates with the expected proportion from an international survey. To determine the predictive validity, we used the Hosmer-Lemeshow test to assess calibration and the C (concordance) index to assess discrimination.

Results. Overall, the predictive validity of the EPC approach to GRADE for the stability of effect estimates was limited. Except for moderate SOE, the expected and observed proportions of stable effect estimates differed considerably. Estimates graded as high SOE were less likely to remain stable than expected by producers and users of systematic reviews. By contrast, estimates graded as low or insufficient SOE were substantially more likely to remain stable than expected. In this sample, the EPC approach to GRADE could not reliably predict the likelihood that individual bodies of evidence remain stable as new evidence becomes available. Depending on the definition used, C-indices ranged between 0.56 (95% CI, 0.47 to 0.66) and 0.58 (95% CI, 0.50 to 0.67) indicating a low discriminatory ability.

Conclusion. The limited predictive validity of the EPC approach to GRADE seems to reflect a mismatch between expected and observed changes in treatment effects as bodies of evidence advance from insufficient to high SOE. In addition, many low or insufficient grades appear to be too strict.

https://www.ncbi.nlm.nih.gov/books/NBK321518/pdf/Bookshelf_NBK321518.pdf

Creating a sound science basis for policy

Goal	Recommended steps to achieve (30 days) (red = essential)
Serve as a source of scientifically sound policy-relevant information	• Address effects caused by interventions • Correct for confounding, measurement error, and model uncertainty • Candidly discuss alternative interpretations of evidence (similar to HEI Review Panel discussions) • Discuss negative as well as positive results • Quantify remaining uncertainties and sensitivities • Restrain overconfidence, confirmation bias • Longer term: Base simulations on validated causal models
Be understandable to a broad audience	• Clearly define all key terms and quantities used to communicate results (e.g., does "Causal" imply that reducing exposure reduces risk?) • Stop conflating association and causation
Facilitate CASAC advice and recommendations	• Consider more of the relevant literature • Longer term: Test causal hypotheses and report the results ○ Is risk conditionally independent of exposure after conditioning on appropriate adjustment sets?

Questions for the CASAC

- *Immediate:* What scientifically valid conclusions can be drawn now (and justified/explicitly derived from data) about how future changes in PM2.5 would change public health risks?
- What relevant data should/must be considered, beyond the 8 key association studies in the Draft ISA/PA?
  - Greven et al. 2011, Pun et al. 2017, Henneman et al. 2017, Burns et al. 2019, others in Public Comments?
  - Others?

Questions for the CASAC

- Risk communication
  - What can we say now about policy-relevant implications of data without over- or under-stating what is known?
  - What alternative interpretations should be considered?
  - How should uncertainty best be characterized (quantitatively and accurately)?
- Research needs
  - Correcting for confounding, exposure estimation errors, model uncertainty, etc.
  - How should valid causal simulation models be built, validated, and applied while characterizing remaining uncertainties? (Drs. Aliferis and North comments)
  - What other data (if any) should be collected?